Contralateral Cerebro-Cerebellar White Matter Pathways for Verbal Working Memory: A Combined Diffusion Spectrum Imaging and fMRI Study

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Synopsis

Diffusion spectrum imaging was employed to establish structural connectivity between cerebro-cerebellar regions co-activated during verbal working memory. IFG, IPL, pons, thalamus, superior cerebellum and inferior cerebellum were used as seed points to reconstruct the white matter cerebro-cerebellar circuitry. The reconstructed pathways were examined further to establish the relationship between structural and effective connectivity as well as the relationship between structural connectivity and verbal working memory performance. It was found that structural connectivity is indirectly related to effective connectivity but does not predict it. Additionally, it was demonstrated that the integrity of the ponto-cerebellar tract is an important factor in explaining individual differences in verbal working memory. The findings of the study furthered our understanding of the relationship between structural and functional connectivity and provided insight to the variability in verbal working memory performance.

Introduction

The cerebro-cerebellar model of verbal working memory (VWM)[1] includes the inferior frontal-superior cerebellum network and the inferior parietal-inferior cerebellum network as demonstrated by functional neuroimaging and brain stimulation [1,2,3]. However the structural connectivity for these networks has yet to be verified in humans, therefore the current study aimed to clarify whether cerebro-cerebellar co-activations observed during VWM have anatomical connectivity. We performed anatomically-guided deterministic tractography that used a fiber tracking algorithm with quantitative anisotropy to trace the following tracts: the left inferior frontal gyrus (IFG) via pons to the right superior cerebellum (sCERE), the left inferior parietal lobule (IPL) via pons to the right inferior cerebellum (iCERE) and the cerebellar tracts via thalamus to the left IFG. Once we reconstructed the connectivity for these tracts, we investigated if their microstructure contributes to the individual differences in VWM performance. We hypothesized that greater white matter integrity of the fronto-cerebellar tracts will be associated with faster response times in VWM, whereas greater white matter integrity of parieto-cerebellar tracts will be associated with higher accuracy rates. In addition, we examined whether the white matter tracts underlying cerebro-cerebellar networks are related to the functional dynamics of the interactions between cerebro-cerebellar regions implicated in VWM. In order to do this, we investigated if Bayesian model selection of DCM models informed by the tractography results will have a higher degree of confidence in model inference than uninformed models. Subsequently, we examined if structural connectivity can predict effective connectivity within this network.

Methods

31 adults (mean age=22.5±1.2 years) performed a VWM Sternberg task (Fig.1) in a 3T MRI scanner with a 32 channel head coil. Participants were right-handed, did not have a history of neurological or psychiatric conditions. Diffusion spectrum imaging data were acquired using: TR=7200ms, TE=136ms, slice thickness=3mm, 45 slices, FOV=220mm. The diffusion weighting was distributed along the grid of 128 directions with a bmax=7000 s/mm^2. FMRI sequence parameters were: TR=2.5s, TE=29ms, FoV=225mm, 48 slices, and 3.5x3.5x3.5mm^3 voxels. MPRAGE image was acquired (1x1x1mm^3 resolution, TR=2.3s, TE=1.9ms, FoV=256mm, distance factor=50%). Standard Dartel preprocessing was conducted in spm12. All DSI analysis was conducted using DSI Studio. Tractography was performed for every tract separately, resulting in 8 different tracts per subject. The tracts were represented in MNI space. For each of the tracts, the mean tract GFA index was generated. Effective connectivity analysis (Fig. 2) was conducted using DCM in spm12 and correlational analysis between structural and modulatory connections was performed.

Results

The reconstructed tracts are presented in Fig.3. Comparison of Bayesian model selection results and the most optimal model are shown in Fig.4. No significant relationship was found between structural and modulatory connectivity for the tracts from fronto-cerebellar and parieto-cerebellar loops. Pearson correlational analysis for white matter tracts and VWM performance showed that only mean GFA for the pons-sCERE tract positively correlated with the response time (r=0.47, p=0.004). None of the other tracts were significantly correlated with the response time or accuracy, but there was a tendency for significance between mean GFA of the IPL-pons tract and accuracy rate (r=0.24; p=0.09).

Conclusion

To the best of our knowledge, this is the first study to demonstrate in vivo structural tract connectivity between the left IFG and the right sCERE, and between left IPL and right iCERE via the pons and thalamus using diffusion spectrum imaging tractography. This demonstrates that there are anatomical connections between cerebro-cerebellar regions involved in VWM. We found that structural connectivity of the reconstructed cerebro-cerebellar networks relates functionally to VWM in two ways: First, constructed DCM models that resembled the underlying anatomical pathways more closely had a higher degree of confidence in Bayesian model selection. This suggests that structural connectivity is indirectly related to the effective connectivity. Second, it was found that the increasing connectedness of the ponto-cerebellar tract was correlated with increase VWM efficiency, implying that the structure of ponto-cerebellar tract contributes to individual differences in VWM.

Acknowledgements

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References

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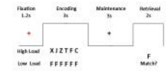
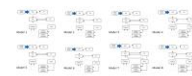
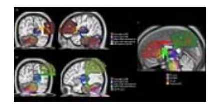
Figures



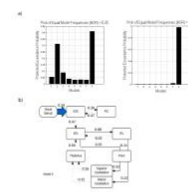
Sternberg's verbal working memory task



DCM models informed by the tractography results specified for effective connectivity analysis



Tracts reconstructed in the study: A) IFG-pons-cerebellum-thalamus-IFG network, B) IPL-pons-cerebellum network, c) reconstructed cortico-subcortical white matter pathways from verbal working memory network



DCM results: A) Protected exceedance probability for 8 specified models uninformed (left) and informed (right) by tractography results; B) The optimal Model 8 informed by tractography results. Dotted lines indicate intrinsic effects, continues lines represent the modulatory effects. Driving input is indicated by the blue arrow.